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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,351	07/30/2001	Makoto Asashima	31671-173644	1990

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,351	ASASHIMA ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 March 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/19/03 has been entered as paper #11.

The amendment, and response filed 3/19/03 have been entered as paper #13. Claims 18-24 have been cancelled, claims 25-27 are pending in the application and under current examination.

Unless otherwise indicated, previous objection and rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The argument would be addressed to the extend that apply to the present rejections.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, and the rejection has been modified as follows.

Claims 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transplanting to a developing xenopus fetus an *in vitro* induced and stage-matching organ of the xenopus, does not reasonably provide enablement for transplanting to a developing fetus of any vertebrate species an *in vitro* induced and stage-specific organ of the species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Claims are drawn to a method of transplanting an *in vitro induced organ* into a recipient *vertebrate* of the *same species* comprising, i) determining the stage of a

recipient vertebrate, ii) culturing an organ induced from ectoderm region which has been cut off from the blastula to the same stage as that of the recipient, and iii) transplanting the cultured in vitro induced organ into the recipient.

With respect to the breadth of the claims, they encompass inducing the formation of an organ in vitro for any vertebrate species at any developmental stage of the embryo. The specification does not specifically define the term, "stage", in light of the teaching of the specification, the stage taught in the specification is the embryonic developmental stages of xenopus, such as those illustrated in figures 1, 2, and 4; and the specification is silent with respect to the stages of neonatal, infant, or adult, therefore, the scope of the claims taught in the specification appears to be limited to transplanting *in vitro* induced organ into the *fetus* of a vertebrate rather than matured vertebrates.

With respect to determining the stage of a recipient vertebrate by genome DNA markers, applicants argue in Paper #13 that stage marker gene DNAs for a number of animals are known such as listed in the databases of "Ontology of Human Developmental Anatomy" or "Kidney Development Gene Expression Database". The arguments and evidence have been fully considered but they are not persuasive. The data in these databases are limited to human, mouse, and rat, they are not representative species of the vertebrate genus, because approximately 45,000 living species constitute the vertebrates and about 400 species constitute the amphibians (the subgenus that includes Xenopus). Even for urodele (belongs to amphibians as does Xenopus), the inventors acknowledge that "LITTLE IS KNOWN ABOUT THE MOLECULAR

BACKGROUND OF URODELE EMBRYOS" (right column, page 115, Ariizumi et al, Zoological Sci 1999;16:115-24). Therefore, as indicated in the previous Office actions, the skilled artisan could not practice the invention without first carrying out undue experimentation to determine the developmental stage-specific genomic DNA markers for representative species of the broadly claimed genus.

In paper #13, applicants allege that the Examiner does not understand the present invention correctly, that the invention is "*culturing an organ to the same stage as that of the recipient vertebrate, and transplanting the cultured organ which had been induced in vitro into the recipient vertebrate of same species*". In response, the Office acknowledges the concept of the invention and indicates why the specification does not support the full scope of the claimed invention. For the sake of argument, assuming the stage-specific genomic DNA marker is available for the representative species of all vertebrates, there are many other foreseeable or unforeseeable barriers to fully enable the aforementioned steps in vertebrates, which will be discussed in detail as follows.

With respect to culturing an organ induced from ectoderm region that has been cut off from the blastula. First, it is noted that the term "blastula" (step ii of the claim 25) refers to an early *non-mammalian* embryo (as indicated in the PubMed Mesh word), thus, the preamble of the claims (drawn to all vertebrates) is inconsistent with the body of the claims, which are limited to a non-mammal. Second, the specification fails to teach inducing an organ *in vitro* for any mammalian species, thus, fails to provide sufficient support for the full scope of the claimed invention. Accordingly, the claims are limited to non-mammalian vertebrates.

With respect to embryo development *ex vivo*, which are required for *in vitro* organ induction, the report in *ex vivo* organogenesis is scarce if any on *in vitro* induced organ in vertebrates other than amphibians. *Niemann et al* (Theriogenology 2001;56:1291-1304) teach at a post-filing date that the porcine embryos can be cultured in defined medium only to the *blastocyst* stage (abstract). *Watt et al* (Science 2000 Feb;287:142730) review the infant stage of the stem cell biology "THE SPOTLIGHT ON STEM CELLS HAS REVEALED GAPS IN OUR KNOWLEDGE THAT MUST BE FILLED IF WE ARE TO TAKE ADVANTAGE OF THEIR FULL POTENTIAL..., WE NEED TO KNOW MORE ABOUT THE INTRINSIC CONTROLS THAT KEEP STEM CELLS AS STEM CELLS OR *DIRECT THEM ALONG PARTICULAR DIFFERENTIATION PATHWAYS*." *Donovan and Gearhart* (Nat 2001 Nov;414:92-97) teach "IF STEM CELLS ARE TO BE USED TO TREAT A WIDE VARIETY OF HUMAN DISEASES, THEN WE WILL NEED TO OVERCOME SEVERAL FORMIDABLE CHALLENGES. STEM CELLS WILL BE NEEDED IN LARGE QUANTITIES AND BE ABLE *TO DIFFERENTIATED IN A CONTROLLED MANNER* TO FORM HOMOGENEOUS POPULATIONS OF CELLS THAT ARE HISTOCOMPATIBLE WITH AN INDIVIDUAL" (left column on page 95). *Simerly et al* (Science 2003;300:297) report the molecular obstacles in cloning primates, and concludes, "PRIMATE NUCLEAR TRANSFER APPEARS TO BE CHALLENGED BY STRICTER MOLECULAR REQUIREMENTS FOR MITOTIC SPINDLE ASSEMBLY THAN IN OTHER MAMMALS", AND "WITH CURRENT APPROACHES, NT TO PRODUCE EMBRYONIC STEM CELLS IN NONHUMAN PRIMATES MAY PROVE DIFFICULT—AND REPRODUCTIVE CLONING UNACHIEVABLE". *Draper et al* (Curr Opin Obstetrics Gynecol 2002;14:309-15) teach at a post-filing date, "RESEARCH USING MOUSE EMBRYONIC STEM CELLS HAS YIELD PROTOCOLS FOR INDUCING THE DIFFERENTIATION OF EMBRYONIC STEM CELLS INTO A VARIETY OF CELL LINEAGES. HOWEVER, HUMAN PLURIPOTENT STEM CELLS AND MURINE PLURIPOTENT STEM CELLS DIFFER IN VARIOUS RESPECTS, AND IT REMAINS TO BE SEEN WHETHER

THESE PROTOCOLS ARE DIRECTLY TRANSFERABLE TO HPSCs" (last paragraph, page 309). *Draper et al* also review the state of the art for selective in vitro lineage differentiation in mice and humans, and the best result to that date, is obtaining a clumps of cells bearing appropriate surface markers or functional characteristics of the desired cell lineage, not a single organ has been induced (Section in pages 312-313). Apparently, differentiating embryonic stem cells in a controlled manner and *in vitro* induced organ formation has not been realized for vast majority of vertebrates. Even considering the scope of the amphibians, the unpredictable nature of *in vitro* induced organ formation could be seen in a reference newly submitted by the applicants, wherein *Ariizumi et al* (Int. J Dev Biol 1996;40:715-8) teach that using the same protocol, a beating heart could be induced from newt ectoderm but not Xenopus ectoderm (both are amphibians), and concluded "THE INDUCTION PROPERTIES OF ACTIVIN ON NEWT ECTODERM ARE DIFFERENT FROM THOSE ON XENOPUS ECTODEM" (right column, page 716). The specification fails to teach what is unknown in the art, and how to overcome the art-known hurdles, thus, it would have required undue experimentation for the skilled artisan intending to practice the instant invention as it is broadly claimed.

With respect to transplanting the cultured organ into the fetus of the recipient vertebrate, first the specification is silent with regard to how such transplant could be done without disturbing the development of a fetus in a mammal, and bring the fetus to term, which is required for a real world utility of the invention. It is a common knowledge in the art, even minor disturbance could cause abortion of a fetus in a mammal, stage-specific organ transplantation in a mammalian fetus would almost certain leads to the

abortion, and the goal of the method will not be achieved. Second, even if the transplantation could be done, the specification is silent with respect to the graft rejection response since the claims encompass allogeneic transplantation. *Denning et al* (Reproduction 2003;126:1-11) teach that a major initiative for studying ES cells is to direct their differentiation to specific lineages for transplantation, and hence address the current chronic shortage of tissue available for treatment of degenerative disease. "A CRITICAL ISSUE, AS WITH MOST TRANSPLANTS, IS GRAFT REJECTION", "THERAPEUTIC CLONING IS OFTEN SUGGESTED AS A ROUTE TO REDUCING THE EXTENT OF REJECTION...THE AUTHORS NOTE THAT THE EXTENT OF ENGRAFTMENT OF THE *IN VITRO*-DERIVED HSC WAS LOW BECAUSE OF REJECTION BY NATURAL KILLER IMMUNE CELLS, AND THEY SPECULATE THAT EVEN GENETICALLY MATCHED CELLS DERIVED FROM THERAPEUTIC CLONING MAY FACE BARRIERS TO EFFECTIVE TRANSPLANTATION" (right column, page 7). With regard to allogenic transplantation, there are still major barriers for successful transplantation as of post-filing dates. *Weissman* (Science 2000;287:1442-46) teaches that although clinical stem cell transplantation could greatly add to the physician's armamentarium against degenerative diseases, there are still long way to go in reality. The barriers are the complicated immunological responses from the host to the transplanted cells, and the state of primary diseases of these patients. *Game et al* (Wien Klin Wochenschr 2001;113:823-38) detailed different types of allogenic rejection (hyperacute, acute, chronic) and underlying mechanisms involving multiple pathways that lead to the failure of allogenic transplantation, and states, "WHILE MAJOR IMPROVEMENTS HAVE BEEN MADE IN THE PREVENTION AND TREATMENT OF HYPERACUTE AND ACUTE TRANSPLANT REJECTION, MOST GRAFTS WILL SUCCUMB TO CHRONIC REJECTION: THIS REFLECTS THE EXTENT OF OUR KNOWLEDGE OF THE MECHANISMS THAT DRIVE

THESE PROCESSES". The specification fails to teach how to overcome the aforementioned difficulties in the art. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for any stage of any vertebrate recipient, for inducing a functional organ of any vertebrates *in vitro*, and transplanting such to an allogenic embryo, and obtaining a functional organ and a viable fetus, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to *ex vivo* organ induction and transplantation for any and all vertebrates, it would have required extensive undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-27 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite. The preamble of claim 25 recites "to obtain an organ that functions *in vivo*", and the completion of the claim repeats "to obtain an organ that functions in vivo", it is unclear how the transplanting is related to "obtain an organ that functions in vivo", whether the goal of the method is resolved, and whether

the method is for transplantation or obtaining an organ that functions in vivo, thus, the metes and bounds of the claims are uncertain.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 25-27 are newly rejected under 35 U.S.C. 102(a) as being anticipated by *Ninomiya et al* (Develop Growth Differ 1999;41:391-400).

Claims are drawn to a method of transplanting an *in vitro induced organ* into a recipient *vertebrate* of the *same species* comprising, i) determining the stage of a recipient vertebrate using a genomic DNA marker or observation of organ tissues, ii) culturing an organ induced from ectoderm region which has been cut off from the blastula to the same stage as that of the recipient, and iii) transplanting the cultured in vitro induced organ into the recipient.

Ninomiya et al teach culturing an organ induced from ectoderm region which has been cut off from the blastula of a xenopus (abstract). Subsequently, the explants were cultured ex vivo, and used for transplantation (page 393). *Ninomiya et al* teach that the same stage of embryo as the grafts were used as hosts (4th paragraph, page 393). Therefore, *Ninomiya et al* anticipate the instant claims.

It is acknowledged that the foreign priority document has been filed for this application, which has an earlier filing date compared to the cited art. However,

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. An English translation may be filed for the purpose of determining the applicant's right to rely on the foreign filing date.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
August 8, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER